

# **Chemical Composition and Antiplasmodial Activity of the Essential Oil of *Rhododendron subarcticum* Leaves from Nunavik, Québec, Canada**

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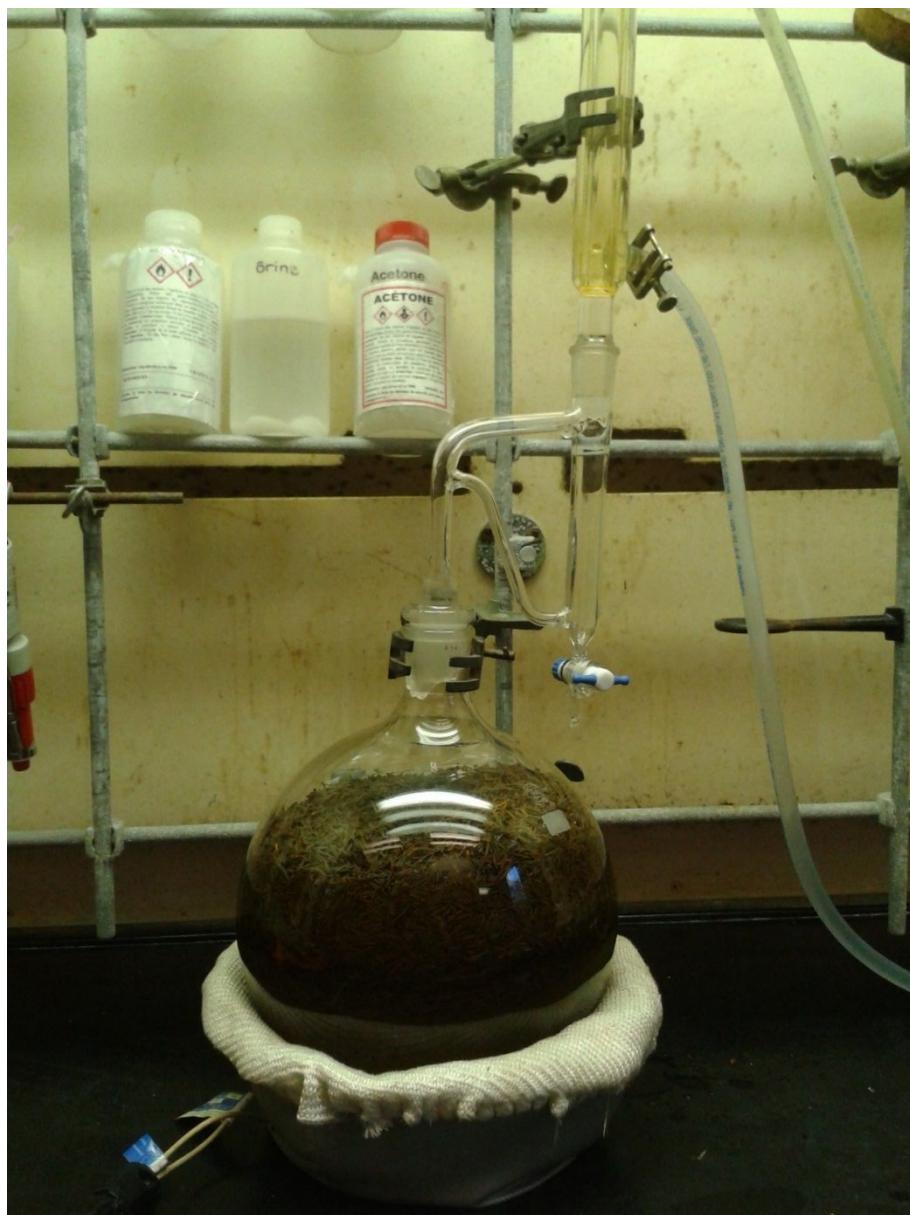
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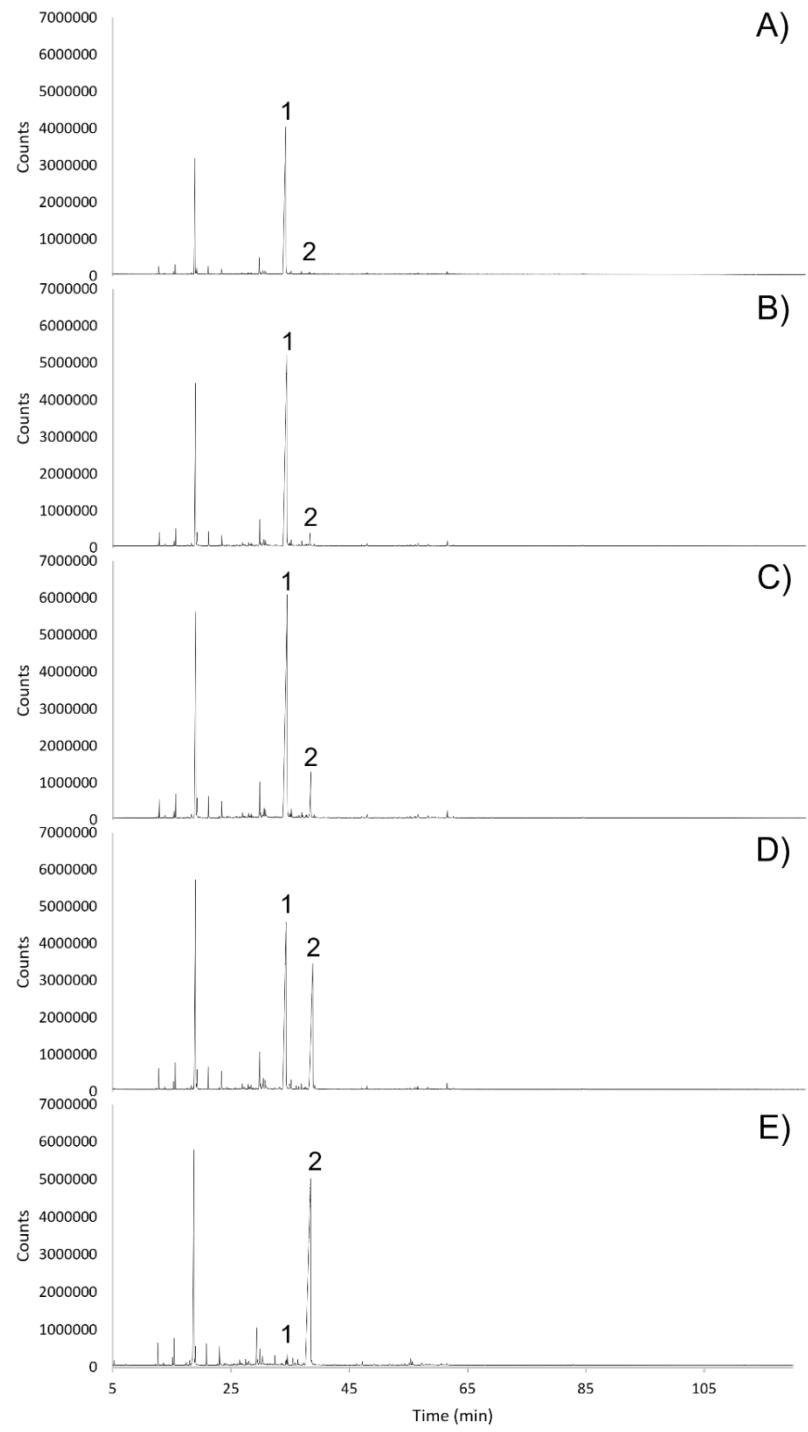
## **SUPPLEMENTARY INFORMATIONS**

## **FIGURES**



**Figure S1.** Hydrodistillation setup with Clevenger apparatus and a 5 L round bottom flask.

Distillation was done with cohobation. During distillation, the flask was covered with aluminium foil.



**Figure S2.** GC-FID chromatograms of *R. subarcticum* essential oil at different inlet temperatures.

A) 170 °C, B) 200 °C, C) 220 °C, D) 250 °C, and E) 300 °C. Assigned compounds are 1. Ascaridole

and 2. Isoascaridole.

## Tables

**Table S1.** GC and MS information on unidentified compounds from *Rhododendron subarcticum*

leaves essential oil.

$M^+$ [a]	m/z <sup>[b]</sup>	LRI exp. (DB- 5MS)	Relative proportion <sup>[c]</sup> [% ± SD]
166 (30)	81 (100), 123 (100), 95 (77), 55 (59), 77 (48), 67 (46), 79 (47), 53 (42), 51 (34), 166 (30)	1149	0,2 ± 0,0
166 (10)	95 (100), 71 (31), 96 (16), 65 (13), 67 (11), 166 (10), 51 (8), 94 (7), 66 (5), 53 (5)	1160	0,2 ± 0,0
150 (53)	91 (100), 79 (85), 107 (82), 77 (74), 150 (53), 51 (48), 105 (47), 53 (32), 117 (30), 93 (28)	1308	0,2 ± 0,0

[a] Molecular ion tentatively identified based on EI GC-MS spectrum (observed m/z, isotopic patterns, fragments) [b] Spectrometric data are presented as a list of the main m/z in the form of m/z (relative abundance). [c] This table lists only unidentified compounds with relative proportions ≥ 0,1 %.

**Table S2.** Retention indices on polar column according to FAMEs and FAEEs standards series for compounds identified in the essential oil obtained from the leaves of *Rhododendron subarcticum* Harmaja from Boniface river region in Nunavik.

Compounds	LRI	
	(polar column) <sup>[a]</sup>	
	exp.	lit. <sup>[b]</sup>
$\alpha$ -Thujene	396/423	-
$\alpha$ -Pinene	393/420	393/427
Camphene	419/452	-
Sabinene	462/506	-
$\beta$ -Pinene	450/491	460/505
1-Octen-3-ol	821/864	814/858
Myrcene	512/569	513/567
$\alpha$ -Phellandrene	507/564	522/574
$\delta$ -3-Carene	489/541	-
$\alpha$ -Terpinene	524/585	529/586
<i>p</i> -Cymene	635/678	635/678

Limonene	547/607	553/608
$\beta$ -Phellandrene	560/614	-
( <i>Z</i> )- $\beta$ -Ocimene	603/639	-
( <i>E</i> )- $\beta$ -Ocimene	615/653	-
$\gamma$ -Terpinene	608/646	612/654
Terpinolene	640/681	638/681
<i>p</i> -Cymenene	800/843	753/802
Linalool	919/961	913/956
<i>n</i> -Nonanal	755/804	751/800
1,3,8- <i>p</i> -Menthatriene	784/829	-
dehydro Sabina ketone	998/1041	-
cis- <i>p</i> -Menth-2-en-1-ol	989/1032	-
trans-Pinocarveol	1011/1054	-
trans- <i>p</i> -Menth-2-en-1ol	924/966	-
Camphor	866/908	-
Pinocarvone	919/961	-
Borneol	1059/1101	-
Terpinen-4-ol	962/1004	959/1002
Thuj-3-en-10-al	980/1023	-
Cryptone	1019/1061	-

Myrtenal	977/1020	-
$\alpha$ -Terpineol	1059/1101	1043/1087
<i>p</i> -Cymen-8-ol	1209/1250	1188/1231
Estragol	1029/1071	1018/1062
Myrtenol	1149/1189	-
Ascaridole	1072/1114	-
cis-Piperitone epoxide (epoxide vs IPP)	1080/1121	-
Carvenone oxide	1067/1109	-
Phellandral	1067/1109	-
Bornyl acetate	935/977	942/984
<i>p</i> -Cymen-7-ol	1453/1491	-
Thymol	1532/1569	-
Carvacrol	1571/1607	1565/1601
Isoascaridole	1207/1248	1178/1222
<i>p</i> -Mentha-1,4-dien-7-ol	-	-
Citronellyl acetate	-	-
trans-Geranyl acetate	-	-
Aromadendrene	989/1032	953/1000
( <i>E</i> )- $\beta$ -Farnesene	-	-
Caryophyllene oxide	1312/1351	1325/1364

14-Hydroxy-( <i>Z</i> )-caryophyllene	-	-
Germacrone	1553/1588	-
[ <sup>a</sup> ] LRI values on polar column obtained according to standards of FAEEs /FAMEs; [ <sup>b</sup> ] Databases LRI shown for polar column are values from FFNSC 3 <sup>1</sup> .		

**Table S3.** Relative proportions observed by analysis with GC-FID of *R. subarcticum* essential oil at different GC inlet temperatures.

Compounds	LRI	Relative proportions			Difference
		(Non-polar column)	(% ± SD) 170 °C	220 °C	
α-Thujene	922	0.1	0.1	0.0	
α-Pinene	928	0.9 ± 0.1	1.2	0.3	
Camphene	943	0.1	0.2	0.1	
Sabinene	968	0.3	0.5	0.2	
β-Pinene	972	1.2 ± 0.1	1.4	0.3	
1-Octen-3-ol	978	tr	tr	0.0	
Myrcene	987	tr	tr	0.0	
α-Phellandrene	1003	tr	0.1 ± 0.0	0.1	

$\delta$ -3-Carene	1004	tr	$0.1 \pm 0.0$	0.0
$\alpha$ -Terpinene	1013	$0.2 \pm 0.0$	$0.5 \pm 0.0$	0.3
<i>p</i> -Cymene	1025	$21.1 \pm 1.0$	$19.8 \pm 0.2$	-1.3
Limonene	1026	$0.2 \pm 0.0$	$0.3 \pm 0.1$	0.1
$\beta$ -Phellandrene	1027	$1.0 \pm 0.1$	1.0	-0.1
( <i>Z</i> )- $\beta$ -Ocimene	1034	tr	0.1	0.1
( <i>E</i> )- $\beta$ -Ocimene	1044	tr	tr	0.0
$\gamma$ -Terpinene	1054	1.0	1.7	0.6
Terpinolene	1080	0.1	0.2	0.1
<i>p</i> -Cymenene	1085	0.7	1.2	0.5
Linalool	1099	0.1	0.3	0.2
<i>n</i> -Nonanal	1103	tr	0.2	0.1
1,3,8- <i>p</i> -Menthatriene	1107	tr	0.1	0.1
Dehydro sabina ketone	1112	tr	0.1	0.1
cis- <i>p</i> -Menth-2-en-1-ol	1118	tr	0.2	0.2
trans-Pinocarveol	1133	0.1	0.5	0.5
trans- <i>p</i> -Menth-2-en-1ol	1135	$0.2 \pm 0.0$	0.1	-0.1
Camphor	1138	$0.1 \pm 0.0$	0.1	0.1
Pinocarvone	1154	0.1	0.4	0.3
Borneol	1164	0.1	0.1	0.1

Terpinen-4-ol		1176	2.5	3.0	0.5
Thuj-3-en-10-al		1177	0.3	0.2 ± 0.1	0.0
Cryptone		1179	tr	tr	0.0
Myrtenal		1187	0.4 ± 0.4	0.7 ± 0.1	0.3
$\alpha$ -Terpineol		1189	0.4 ± 0.4		-0.4
<i>p</i> -Cymen-8-ol		1190	0.4	1.1 ± 0.1	0.7
Estragol		1192	0.2		-0.2
Myrtenol		1194	tr	tr	0.0
Ascaridole		1245	64.7 ± 0.7	39.1 ± 1.0	-25.6
cis-Piperitone (epoxide vs IPP)	epoxide	1250	0.3 ± 0.1	0.4	0.1
Carvenone oxide		1254	0.5 ± 0.1	0.6	0.1
Phellandral		1270	0.1	0.3	0.2
Bornyl acetate		1278	0.4	0.1	-0.3
<i>p</i> -Cymen-7-ol		1287	tr	0.2	0.2
Thymol		1290	0.1	tr	-0.1
Carvacrol		1297	0.2	tr	-0.2
Isoascaridole		1299	0.3	19.8 ± 1.0	19.5
<i>p</i> -Mentha-1,4-dien-7-ol		1322	tr	tr	0.0
Citronellyl acetate		1347	tr	tr	0.0
trans-Geranyl acetate		1375	tr	tr	0.0

Aromadendrene	1447	tr	0.2	0.2
( <i>E</i> )- $\beta$ -Farnesene	1448	tr	tr	0.0
Caryophyllene oxide	1566	0.1	0.1	0.0
14-Hydroxy-( <i>Z</i> )- caryophyllene	1670	tr	tr	0.0
Germacrone	1676	0.4	0.5	0.1

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tr : Compounds with relative proportions of >0.1% are indicated as traces.

**Table S4.** Taxonomy in previously reported volatile extracts and essential oils from *L. palustre* and synonyms or close relatives

Taxon name used	Origin	Publication year	Extraction method	Main components	Reference
<i>Rhododendron tomentosum</i> Harmaja (previously known as <i>Ledum palustre</i> L.)	Finland	2019	Hydrodistillation	Palustrol, ledol	[2]
<i>Rhododendron tomentosum</i> Harmaja (previously known as <i>Ledum palustre</i> L.)	Poland	2019	Hydrodistillation	$\gamma$ -terpineol	[2]
<i>Rhododendron tomentosum</i> Harmaja ( <i>Ledum palustre</i> )	Poland	2017	Hydrodistillation	Depends on the bioreactor	[3]
<i>Rhododendron tomentosum</i> Harmaja (formerly <i>Ledum palustre</i> L.)	Poland	2016	Hydrodistillation	$\gamma$ -terpineol, palustrol, ledol	[4]
<i>Rhododendron tomentosum</i> Harmaja (formerly <i>Ledum palustre</i> L.)	Poland	2018	Hydrodistillation	-	[5]
<i>Rhododendron tomentosum</i> (Stokes) Harmaja ( <i>Ledum palustre</i> Linnaeus)	Lithuania	2020	Hydrodistillation	Ledol, palustrol ou ledol, palustrol, ascaridole	[6]

<i>Rhododendron tomentosum</i> L. (Stokes) H. Harmaja (formerly <i>Ledum palustre</i> )	Lithuania	2012	Hydrodistillation	p-cymene, ascaridole, palustrol, ledol	[7]
<i>Rhododendron tomentosum</i> Harmaja (previously entitled by several different names)	Lithuania	2020	Hydrodistillation	Palustrol, ledol, ascaridole	[8]
<i>Rhododendron tomentosum</i> (Stokes) H. Harmaja (formerly <i>Ledum palustre</i> Linnaeus)	Lithuania	2011	Hydrodistillation	Palustrol, ledol	[9]
<i>Rhododendron tomentosum</i> Harmaja	Estonia	2014	Simultaneous distillation- extraction	palustrol, ledol, $\gamma$ - terpineol, p-cymene	[10]
<i>Ledum palustre</i>	Netherland	1981	Steam distillation	ledol, palustrol, myrtenal	[11]
<i>Ledum palustre</i> L.	North Korea	2006	Hydrodistillation	Sabinene	[12]
<i>Ledum palustre</i> L. (syn. <i>Rhododendron</i> <i>tomentosum</i> Harmaja, <i>R. palustre</i> )	Poland	2020	Hydrodistillation	Ascaridole, p-cymene	[13]

<i>Ledum palustre</i>	Northeast china	2014	-	Bornyl acetate, p-cymene	[14]
<i>Ledum palustre</i> L.	Northeast china	2017	Subcritical fluid extraction	$\alpha$ -thujenol, dehydrosabinaketone, $\beta$ -phellandrene	[15]
<i>Rhododendron tomentosum</i> Harmaja	Finland	2011	Solvant extraction methanol/ethyl acetate/Hexanes	myrcene, ledol, palustrol	[16]
<i>Rhododendron tomentosum</i> Harmaja, formerly named as <i>Ledum palustre</i> L.	Poland	2019	Various methods	Ledol, palustrol, $\gamma$ -terpineol, p-cymene	[17]
<i>Ledum palustre</i> L. ssp. <i>decumbens</i> (Ait.) Hult.	Alaska	1971	-	Germacrone, myrtenal	[18]
<i>Ledum palustre</i> L.	Finland	1971	-	Palustrol, ledol	[18]
<i>Ledum palustre</i> L.	USSR, Siberia	1983	Steam distillation	Limonene	[19]

<i>Ledum palustre</i> L.	Russia, Siberia	1990	Steam distillation	Limonene	[20]
<i>Ledum palustre</i> L.	Russia, Siberia	1990	Steam distillation	Sabinene, $\alpha$ -terpinene	[20]
<i>Ledum palustre</i> L.	Russia, Siberia	1990	Steam distillation	p-cymene	[20]
<i>Ledum palustre</i> L.	Northwest Russia	1979	Steam distillation	-	[21]
<i>Ledum palustre</i> L.	Russia	2014	Hydrodistillation	Palustrol, ledol	[22]
<i>Rhododendron tomentosum</i>	Northeast china	2016	Hydrodistillation	4-thujene, dehydrosabinaketone, $\alpha$ -thujenal, (-)-4- terpineol	[23]
<i>Ledum palustre</i> L.	Lithuania	2011	Hydrodistillation	Ledol, palustrol	[24]
<i>Ledum palustre</i> L.	Lithuania	2008	Hydrodistillation	Ledol, palustrol	[25]
<i>Rhododendron tomentosum</i> , syn. <i>Ledum</i> <i>palustre</i>	Finland	2021	Steam distillation	myrcene, ledol, palustrol	[26]

<i>Rhododendron tomentosum</i> , syn. <i>Ledum palustre</i>	Finland	2021	Supercritical CO <sub>2</sub>	myrcene, ledol, palustrol	[26]
<i>Ledum palustre</i> L.	Lithuania	2015	Hydrodistillation	Palustrol, ledol	[27]
<i>Ledum palustre</i> L.	Lithuania	2015	Supercritical CO <sub>2</sub>	Palustrol, ledol, ascaridole	[27]
<i>Rhododendron tomentosum</i> Harmaja	Northeast China	2017	Hydrodistillation	4-thujene, α-thujenal, (-)-4-terpineol	[28]
<i>Ledum palustre</i> ssp decumbens (Ait.) Hultén	Alaska	2003	Dynamic headspace	Cymene	[29]
<i>Rhododendron tomentosum</i> ssp. <i>subarcticum</i> (Harmaja) G.D. Wallace	Alaska	2022	Dynamic headspace	Cymene	[30]
<i>Rhododendron tomentosum</i> (Stokes) H. Harmaja (formerly <i>Ledum palustre</i> Linnaeus)	Sweden	2005	Steam distillation	palustrol, myrcene	[31]
<i>Rhododendron tomentosum</i> (Stokes) H. Harmaja (formerly <i>Ledum palustre</i> L.)	Sweden	2006	Steam distillation	p-cymene	[32]

<i>Ledum palustre</i> L.	Estonia	2010	SDE (hexanes)	$\alpha$ -terpineol, palustrol, ledol	[33]
<i>Ledum palustre</i> L. var. angustum N. Busch	China	1987	-	Myrtenal, $\beta$ -thujene, p-cymene,	[34]
<i>Ledum palustre</i> L.	-	-	-	Ascaridole	[35]
<i>Ledum palustre</i> L. var. angustum N. Busch	Northeast china	1989	-	ascaridole, p-cymene, myrtenal	[36]

# NMR SPECTRA OF ASCARIDOLE FRACTION ISOLATED FROM *RHODODENDRON SUBARCTICUM* ESSENTIAL OIL

## *SUBARCTICUM* ESSENTIAL OIL

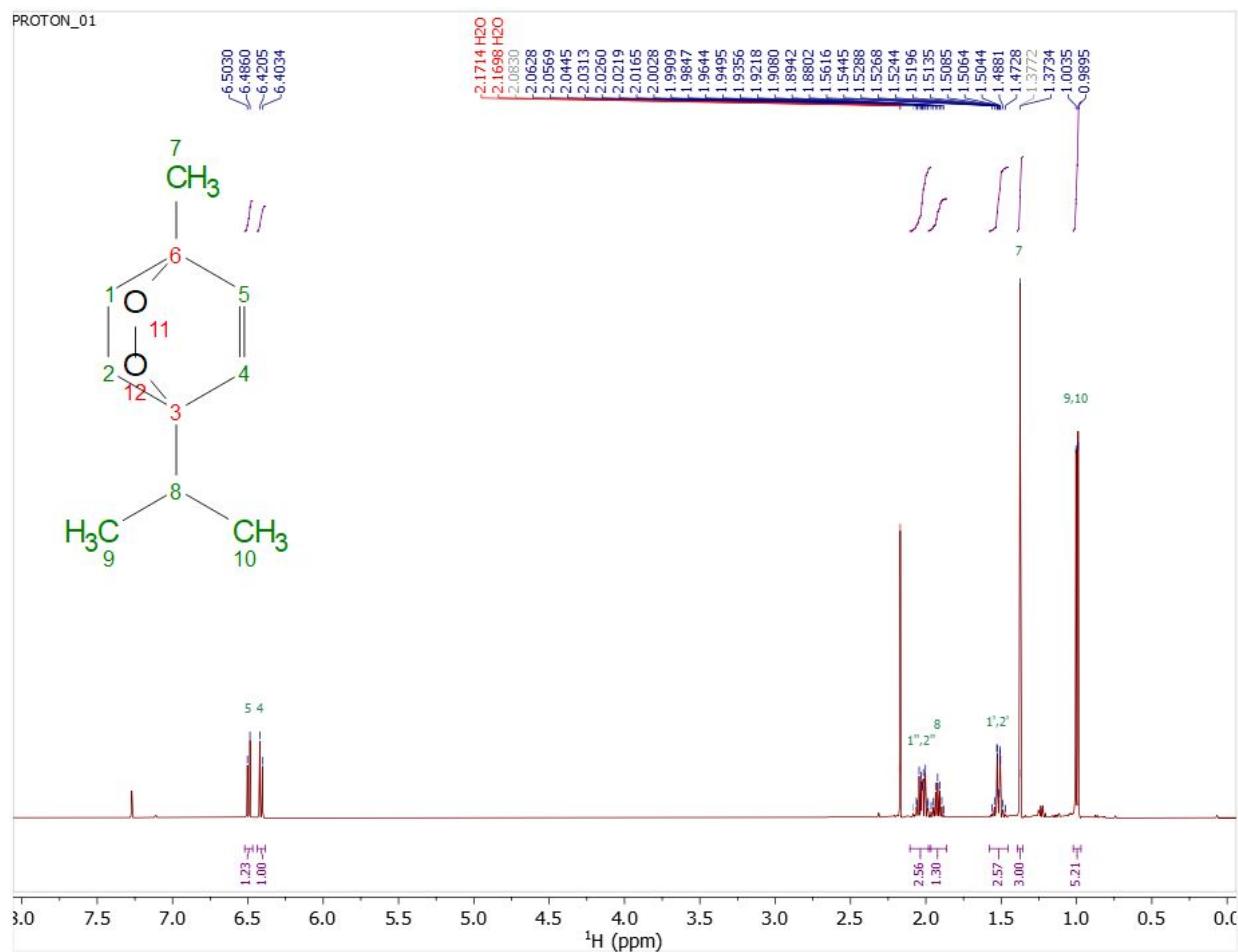


Figure S3. <sup>1</sup>H NMR spectra of ascaridole.

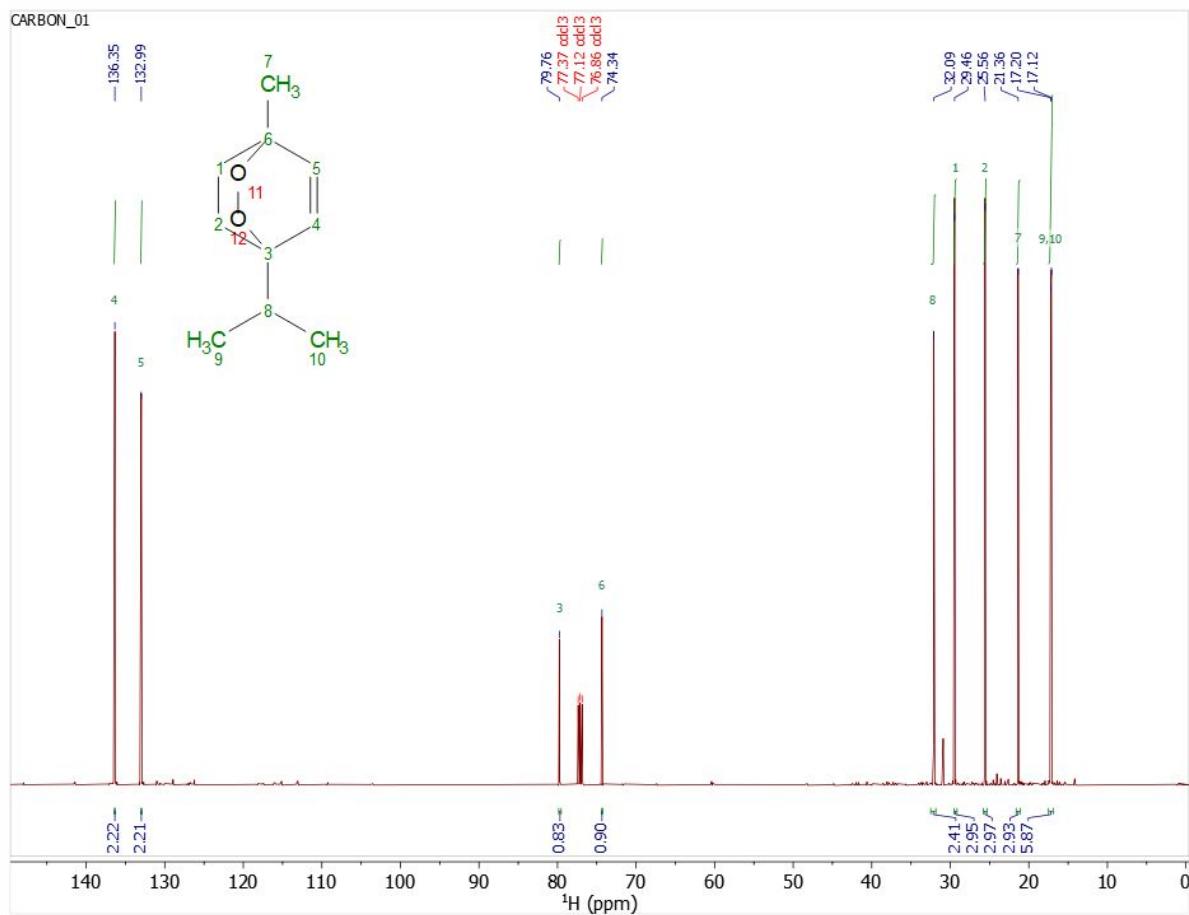
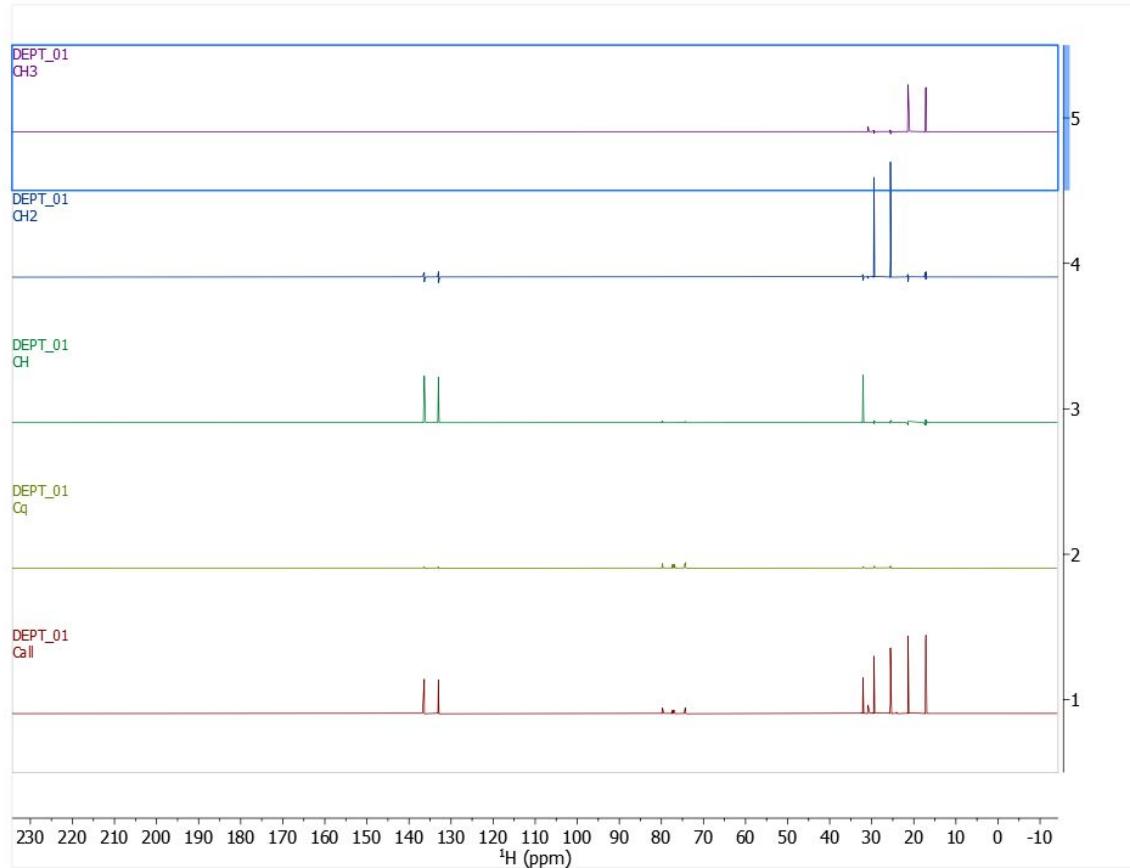


Figure S4.  $^{13}\text{C}$  NMR spectra of ascaridole.



**Figure S5.** DEPT NMR spectra.

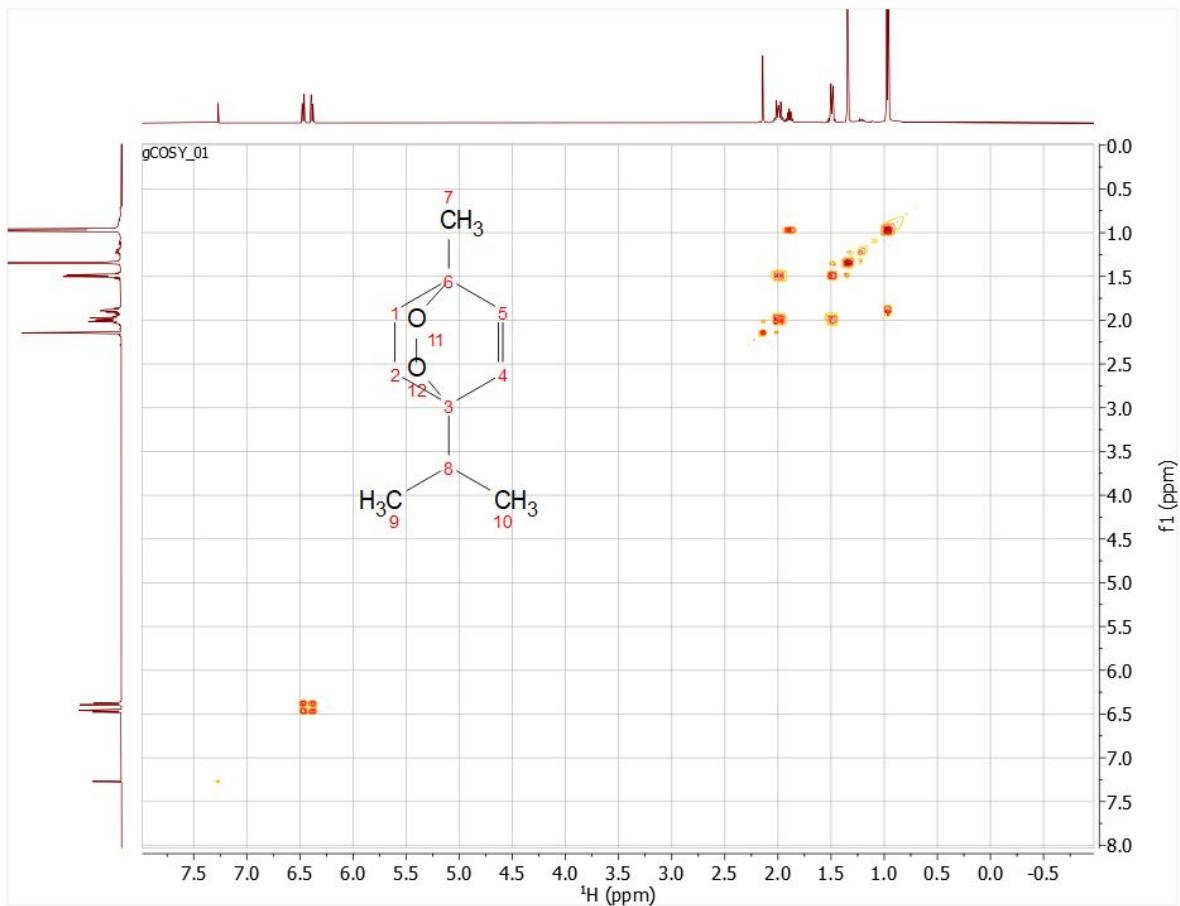


Figure S6. COSY NMR spectra.

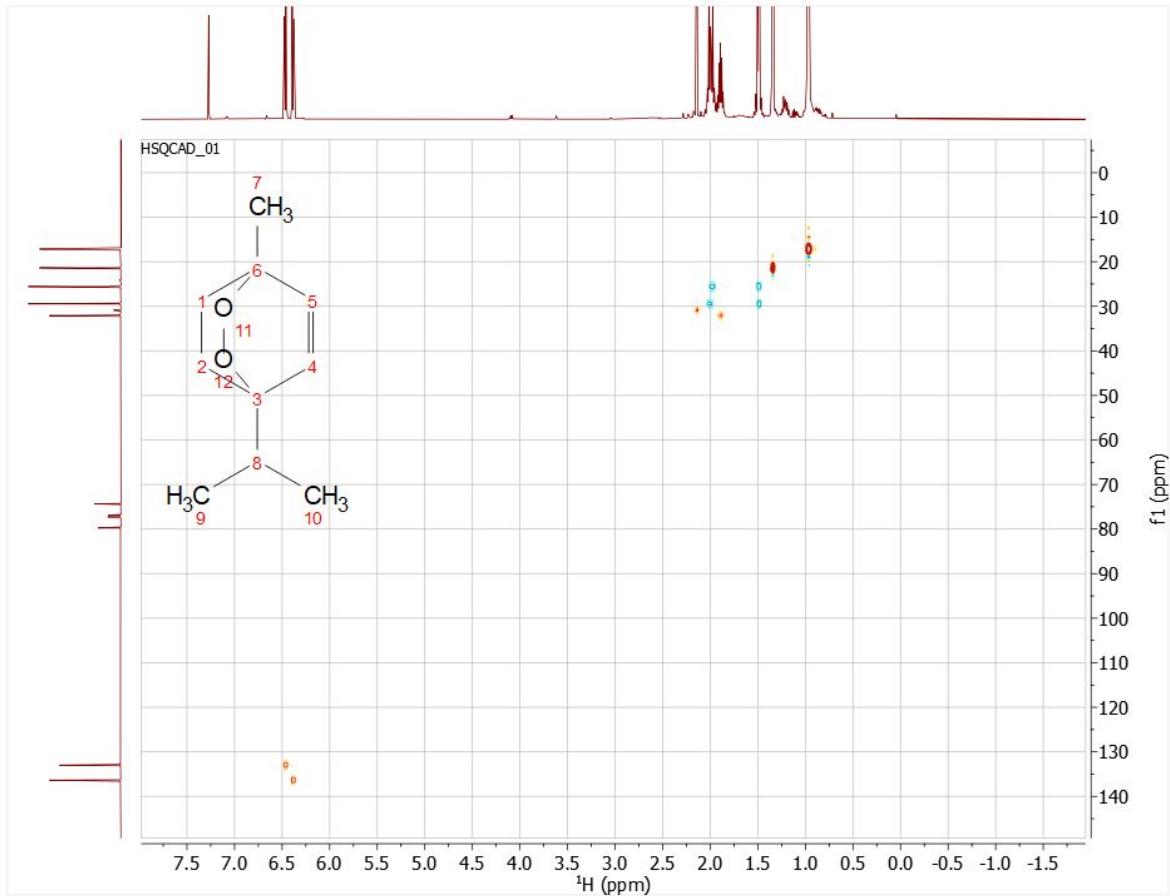


Figure S7. HSQC NMR spectra.

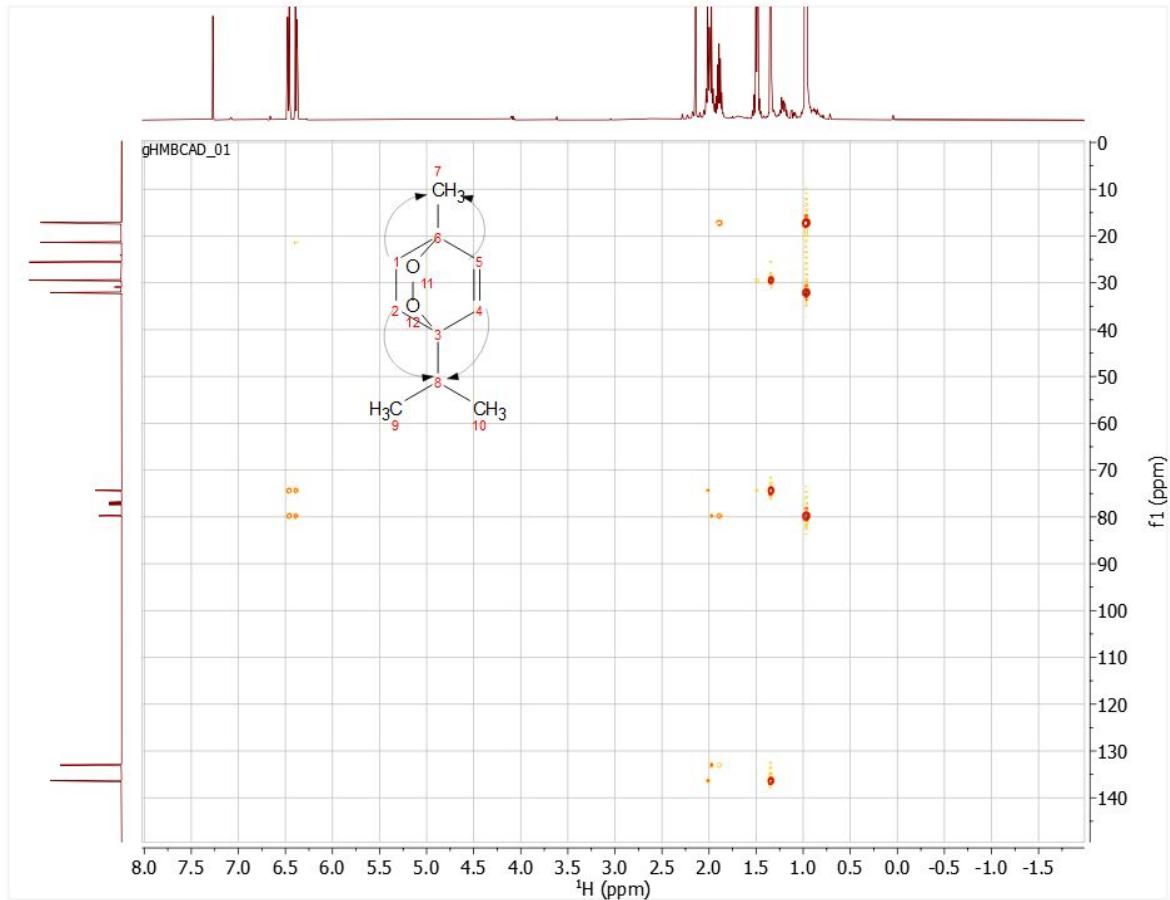
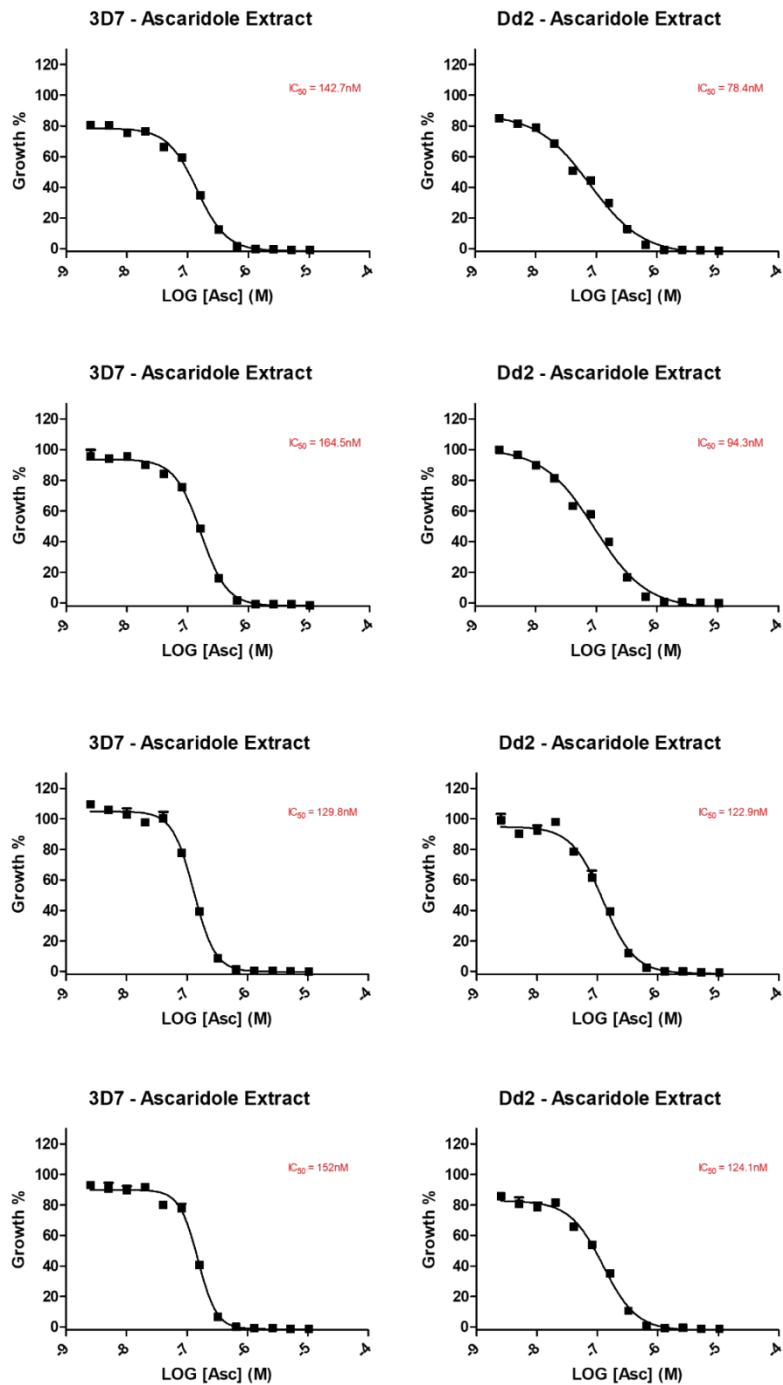


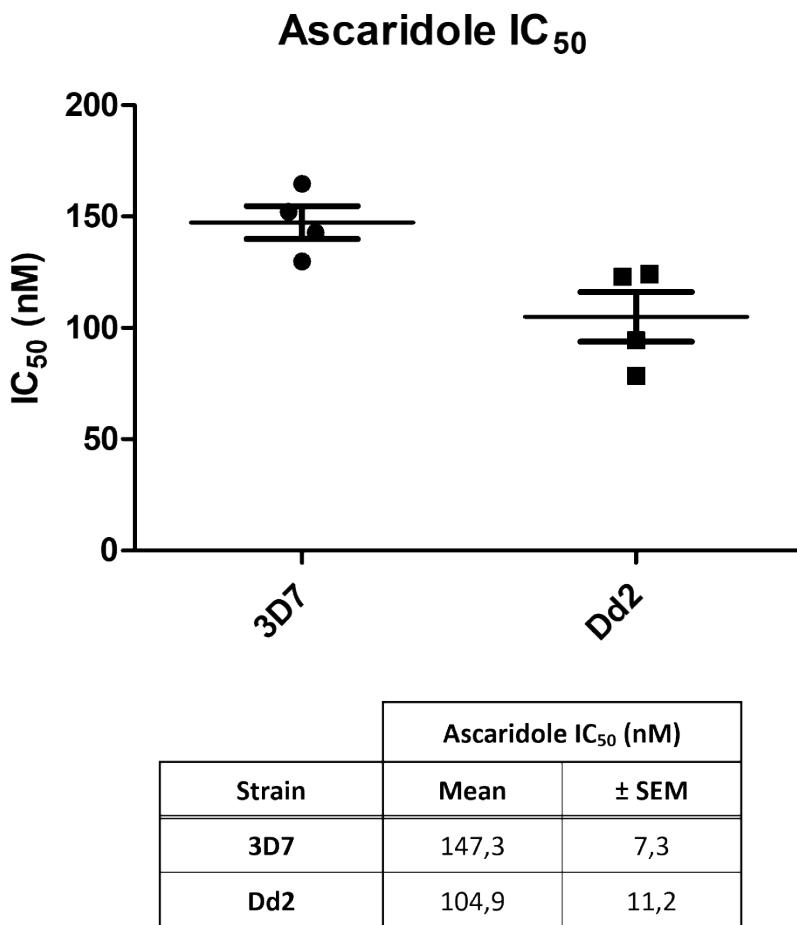
Figure S8. HMBC NMR spectra.

## **ANTIPLASMODIAL ACTIVITY GRAPHICAL REPRESENTATION**

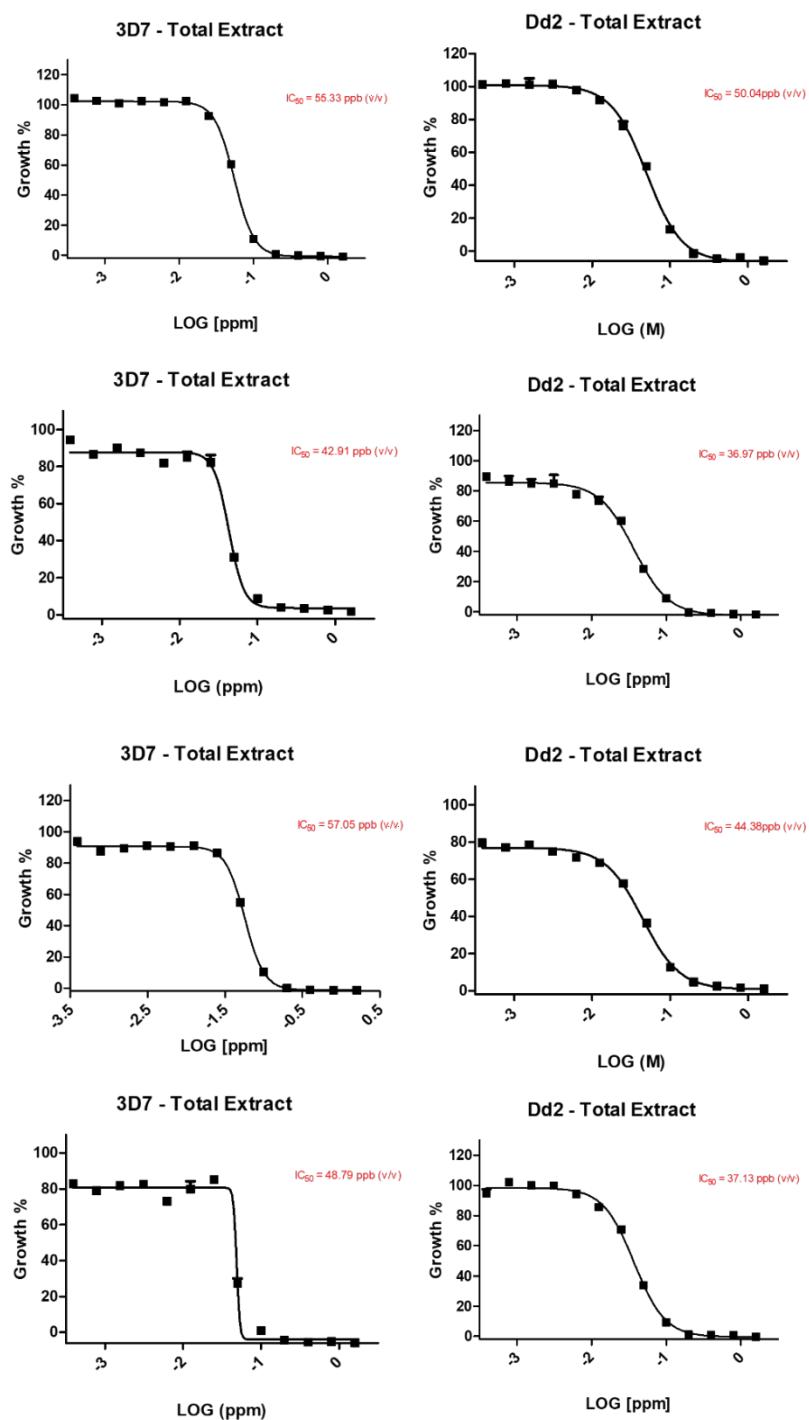


**Figure S9.** Inhibition curves of ascaridole activity against 3D7 and Dd2 *P. falciparum* strains

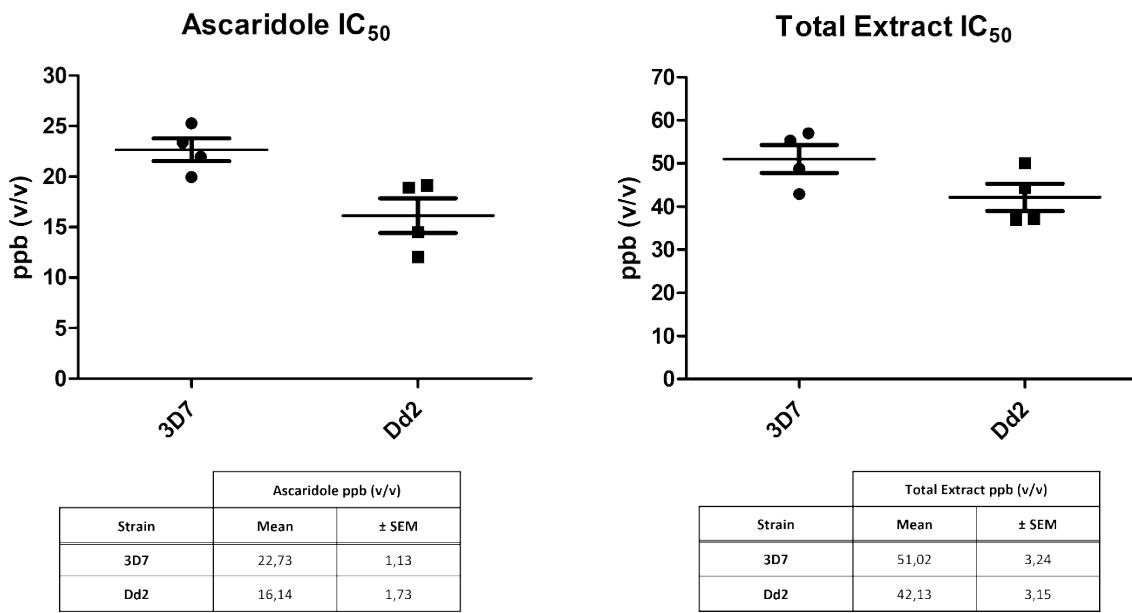
obtained on two assay days, with two replicates per strain on each day.



**Figure S10.** Distribution of IC50 results for ascaridole against 3D7 and Dd2 strains.



**Figure S11.** Inhibition curves of *Rhododendron subarcticum*'s essential oil activity against 3D7 and Dd2 *P. falciparum* strains.



**Figure S12.** Distribution of IC<sub>50</sub> results for ascaridole and *R. subarcticum* essential oil against 3D7 and Dd2 strains.

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